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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/041,958
Filing Date: January 07, 2002
Appellant(s): TZIPORI ET AL.

Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 14, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 26-36 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,080,400	Williams et al	6-2000
5,512,282	Krivan et al	4-1996
WO90/07861	Queen et al	7-1990

Perera et al. Journal of Clinical Microbiology. Vol. 26, No. 10, pp 2127-2131, October 1988.

Engelman et al. Human Hybridomas and Monoclonal Antibodies. New York Plenum Press. pp 23-27, 1985.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A) The rejection of claims 26-36 under 35 U.S.C. 103(a) as being unpatentable over Krivan et al, Perera et al and Williams et al in view of Queen et al, and Engelman et al.

The claims are drawn to a dosage formulation comprising an effective amount of human or humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II *in vivo*, wherein the antibodies are specifically reactive with a single subunit of the Shiga like toxin II produced by *Escherichia coli* which causes hemolytic uremic syndrome, to prevent or treat hemolytic uremic syndrome in a human.

Krivan et al (US Patent Number 5,512,282) teach of purified high titer, monospecific polyclonal antibodies to Shiga-like toxin obtained by a process of inoculating a bovine animal with a purified active SLT derived from *E. coli* and selected from the group consisting of SLT I, SLT II, SLT IIV and mixtures thereof. Krivan et al further teach of the passive immunization of a human or animal against SLT toxinemia

comprising administering to the human or animal a prophylactically effective amount of the elicited antibody. (See claims 1 and 17). Krivan et al further teach that SLT toxinemia can lead to hemolytic uremic syndrome. (See column 1). Krivan et al further disclose that "the present invention provides an antitoxin to one or more SLTs." (See Column 6). Krivan et al further disclose that "A single type of SLT, such as SLT-II or a variant thereof, such as SLT-IIvp can be injected. This provides polyclonal antibodies that are monospecific to just that type of SLT or variant." (See Column 8).

Perera et al (Journal of Clinical Microbiology Vol. 26, No. 10, pp 2127-2131, October 1988) teach of five monoclonal antibodies which bind to the α-subunit of SLT-II and were able to neutralize the toxin. (See abstract).

Williams et al (US Patent Number 6,080,400) set forth that "Studies of Shiga toxin B subunit suggest that neutralizing epitopes may also be present at both the N- and C-terminal regions of VT1 and VT-2 B subunits. Polyclonal antibodies raised against peptides from these regions (residues 5-18, 13-26, 7-26, 54-67, and 57-67) show partial neutralization of Shiga toxin (I Harari and R. Arnon, Carboxy-terminal peptides from the B subunit of Shiga toxin induce a local and parenteral protective effect, Mol. Immunol. 27: 613-621, 1990 and Harari et al, Synthetic peptides of Shiga toxin B subunit induce antibodies which neutralize its biological activity." Williams et al set forth that VT1 and VT2 correspond to SLT-I and SLT-II, respectively. (See columns 5-7).

None of Krivan et al, Perera et al, or Williams et al teach of monoclonal human or humanized antibodies.

Queen et al (WO 90/07861) teach that methodology for the production of CDR-grafted antibodies having CDRs derived from the variable regions of non-human antibodies and framework regions derived from human antibodies were well established in the art at the time the claimed invention was made and the CDR-grafted antibodies were recognized to be useful reagents for diagnostic and therapeutic applications. Queen et al further set forth that humanized antibodies are substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin. (See abstract).

Engelman et al (Human Hybridomas and Monoclonal Antibodies. New York Plenum Press. 1985, pp 23-27) teach that methods for constructing human-human hybrids that secrete human monoclonal antibodies using lymphoblastoid cell lines as fusion partners were well known in the art at the time of Applicants invention.

Given that 1) Krivan et al have taught of methods of passive immunization comprising administering high titer, monospecific polyclonal antibodies against Shiga-like toxin II, and that 2) Perera et al have demonstrated neutralization of SLT-II with monoclonal antibodies which specifically bind the α subunit of SLT-II, and that 3) Williams et al have taught of neutralizing epitopes of the β-subunit of SLT-II, and that 4) Queen et al has taught of the advantages of humanized antibodies over non-human antibodies for therapy in humans, and that 5) Engelman et al has also taught of the advantages of human monoclonal antibodies over non-human monoclonal antibodies for therapy in humans, it would have been prima facie obvious to one of ordinary skill in the art to have generated a humanized antibody or a human monoclonal antibody as

taught by Queen et al and Engelman et al, for use in the method disclosed by Krivan et al. It would have been further obvious to select antibodies against a single α or β subunit in view of Perera et al and Williams et al demonstration of neutralizing monoclonal antibodies against these specific subunits. One would have been motivated to produce such an antibody based on the advantages described by Queen et al and Engelman et al, (i.e., substantially decreased immunogenicity).

It is noted that the references do not teach the amount of antibodies set forth in claims 34 or 36. However, determining the precise dosage of a humanized antibody is merely the result of optimizing a result effective variable. As set forth in In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219, (CCPA 1980), it is normally within the skill in the art to optimize a result effective variable.

(11) Response to Argument

ARGUMENTS:

Apellants argue that the prior art fails to teach any guidance as to the selection of antibodies to Shiga toxin II only to treat or prevent HUS, or antibodies to a single subunit of Stx2 can be effective in preventing or treating disease (not just in a diagnostic assay) and what constitutes and effective dosage of these antibodies. Appellants further assert that it would not have been obvious from studies using animals such as mice what an effective dosage would be, since mice are very resistant to infection, requiring many times more toxin to become sick, than humans. Appellants further assert that only studies in pigs or humans can be used to determine the critical

components of the disease causing etiological agent, what compounds would be effective to treat these critical components and what the effective dosage of these compounds would be. Appellants further assert that Krivan says his antibodies "are not, and cannot be, useful in humans." Appellants have further supplied multiple Declarations setting forth that the neonatal gnotobiotic piglet is the only animal model for infections with E. coli 0157:H7, and has potential for evaluating prophylactic or therapeutic approaches for HUS. Appellants have further supplied a Declaration by Dr Tzipori setting forth that "Unquestionably, polyclonal antibodies made in animals, however purified, cannot be injected into the blood stream of humans, either for treatment or prevention." Appellants conclude that dosage Krivan provides for is for oral administration; not paraenteral, and that this amount 100 mg to 5 grams, greatly exceeds the amount that would be parenterally administered to a child.

RESPONSE:

First, Apellants argue that the prior art fails to teach any guidance as to the selection of antibodies to Shiga toxin II only to treat or prevent HUS, or antibodies to a single subunit of Stx2 can be effective in preventing or treating disease (not just in a diagnostic assay) and what constitutes and effective dosage of these antibodies. However, as set forth in Krivan et al, the claims are directed towards methods of treatment of SLT toxemia (which as set forth in column 1 can progress into HUS) in a human comprising administering a purified, high titer, monospecific antibody which specifically binds a toxin selected from the group consisting of SLT I, SLT II, SLT IIV

and mixtures thereof. Krivan further sets forth that "A single type of SLT, such as SLT-II or a variant thereof, such as SLT-IIvp can be injected." (See column 8). This clearly provides support for using antibodies reactive with only Shiga toxin II. Furthermore, Perera et al demonstrate the generation of five monoclonal antibodies towards Shiga toxin II α-subunit, and each of these monoclonal antibodies was determined to be a neutralizing antibody. Neutralizing antibodies, by definition, neutralize the effect of the toxin, consequently motivation to specifically incorporate antibodies with this property would be readily apparent to one of ordinary skill in the art. Lastly, Appellants assert that the prior art fails to disclose what an effective dosage of these antibodies would be. However, Krivan et al set forth that the usual dosage range would be 100 mg to 5 gm of immunoglobulin. (See column 10). FDA approval, is not a prerequisite for finding a compound useful within the meaning of patent laws. (*Scott [v. Finney]*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed Cir. 1994)]. Office personnel should not require that an applicant demonstrate that a therapeutic agent based on a claimed invention is safe or fully effective drug for humans. (*In re Sichert,* 556 F.2d 1154, 196 USPQ 209 (CCPA 1977).

Second, Apellants further assert that it would not have been obvious from studies using animals such as mice what an effective dosage would be, since mice are very resistant to infection, requiring many times more toxin to become sick, than humans. However, FDA approval of any drug requires human experimentation during phase trials to determine precise effective dosages. Appellants own Declaration illustrates this exact point. Dr. Tzipoir's Declaration, number 6, sets forth that "it will take 10-12 years to determine the effective dose through Phase II/III clinical trials in humans." The point

being, the precise dosage is attainable by those of ordinary skill in the art, the fact that it may take several years does not make it excessive experimentation, given that any drug wanting to receive FDA approval is required to undergo the same process. Additionally, Appellants have questioned whether Williams et al is even prior art against the instant application. However, the only teaching relied upon by Williams is a reference to published work carried out in 1990, well before Applicants filing date. To fully demonstrate the teachings of Williams are entitled to the filing date of the CIP application, page 9 of the CIP Application, 08/410,058 is enclosed. This page demonstrates verbatim support of the text relied upon in the rejection.

Third, Appellants further assert that only studies in pigs or humans can be used to determine the critical components of the disease causing etiological agent, what compounds would be effective to treat these critical components and what the effective dosage of these compounds would be. However, as set forth above studies in humans are required for FDA approval of any drug to be administered to humans. Furthermore, practicing the claims of Krivan et al (i.e., claims 17-18) require this routine experimentation to be done.

Fourth, Appellants further assert that Krivan says his antibodies "are not, and cannot be, useful in humans." However, Appellants have not appreciated what Krivan is in fact teaching. Appellants have quoted from Krivan et al "animals to be ***treated to make*** antibodies do not possess receptors for the toxin" (thereby excluding humans). (Emphasis added). This is a rather humane teaching. Simply put, Krivan is advising eliciting (making) an antibody in an animal which does not have receptors for the toxin,

thereby sparing the animal unnecessary pain. This has nothing to do with the elicited antibody then being used in an animal which possesses receptors for the toxin (e.g., humans) as exemplified in the claims.

Fifth, Appellants have further supplied multiple Declarations setting forth that the neonatal gnotobiotic piglet is the only animal model for infections with E. coli 0157:H7, and has potential for evaluating prophylactic or therapeutic approaches for HUS. However, as set forth above, the gnotobiotic piglet is not required to determine the effective dosage of the resulting antibodies to Shiga toxin II. As set forth in the Declaration by Dr. Tzipori, point 6, this effective dosage can be determined through Phase II/III clinical trials in humans.

Sixth, Appellants have further supplied a Declaration by Dr Tzipori setting forth that "Unquestionably, polyclonal antibodies made in animals, however purified, cannot be injected into the blood stream of humans, either for treatment or prevention." However, Applicants are again directed to the previously submitted CDC Drug Service showing Diphtheria Equine Antitoxin (intended for human use) which is a sterile, aqueous solution of the refined and concentrated proteins, chiefly globulins, containing antitoxic antibodies from the blood serum of horses that have been immunized against diphtheria toxin.

Finally, Appellants conclude that dosage Krivan provides for is for oral administration; not paraenteral, and that this amount 100 mg to 5 grams, greatly exceeds the amount that would be parenterally administered to a child. However, Appellants have not considered the full teachings of Krivan et al. First, Krivan et al set

forth that the antibodies of the invention are administered "locally, as by injection or topical application, intravenously, orally, intradermally, subcutaneously, intraocularly, subconjunctively, intramuscularly, and intrathecally." (See column 11). Lastly, Appellants assert that the amount referenced by Krivan et al greatly exceeds the amount that would be parenterally administered to a child, however Appellants will appreciate that not a single one of the rejected claims recites a "child."

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Mark Navarro
Primary Examiner
November 23, 2004

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